Written Comments to the National Research Council

Evaluation of the Protocol for the IRIS Toxicological Review of Inorganic Arsenic

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These comments are submitted on behalf of the US Small Business Office of Advocacy (Advocacy) about the May 2019 draft EPA problem formulation and systematic review protocol for arsenic. We urge the committee to read carefully and address the public comments on the protocol and to advise EPA to integrate better the 2013 NRC recommendations. This specifically includes addressing low dose exposures, and the mode of action (MOA) at low doses.

Advocacy commented on arsenic cancer assessment as early as 2001, when EPA initially considered lowering the drinking water standard from 50 ug/L to 10 ug/L. At that time, we expressed concern that the evidence supporting a significant risk below 50 ug/L was in substantial question. This standard potentially affects tens of thousands of small and very small water systems in the United States.

In the last two decades, much more evidence has come forth supporting a drinking water threshold at greater than 50 ug/L. In my 2010 testimony before the EPA Science Advisory Board, I raised many of the concerns that are still unaddressed by the agency, now almost over two decades. EPA staff, as in 2010 and 2014, appear reluctant to seriously consider the mass of scientific evidence that points to the existence of a threshold effect, including the mechanistic and epidemiologic evidence developed during the last two decades. Commenters have described a number of epidemiologic and ecological studies of lung and bladder cancer that point to a threshold in the neighborhood of 50 to 150 ug/L. Some have explained the current overestimation of risk as attributable to exposure misclassification, and confounding issues such as nutritional deficiency and other lifestyle factors. If the IRIS assessment is to reflect the best available world class science, the NAS needs to send a clear and explicit message to the agency that it must seriously implement the 2013 NRC recommendations.

In 2010, EPA presented a linear low dose extrapolation in a draft (since withdrawn) that relied upon a high-dose comparison population for 98% of the statistical power and that

was only mildly influenced by the low-dose Southwest Taiwan villages. Further, EPA stated, without explanation, that it was not appropriate to use alternative models that do find "insignificant or negative dose-response" relationships in the low-dose range. The EPA analysis was universally criticized by the public commenters. This led to the 2013 NRC arsenic report recommendations, which directed EPA to reflect more on mode-of-action data and threshold dose response relationships.

Fast forward to 2019, and there is little evidence that EPA plans to reflect upon the threshold-based evidence. The agency continues to develop new reasons for to avoid considering MOA data. As one commenter stated, EPA has already decided in this protocol that it would be calculating OSF or IUR values, which assumes a linear dose-response. EPA finds that it is too difficult to incorporate MOA concepts into the dose-response derivation, and instead will rely on newly developed Bayesian meta- regression analyses (with methodological approaches that are highly uncertain). As commenters have pointed out, unless EPA removes the high-dose data from the analysis, it is likely to end up with the same results – that the high dose data will again dominate the risk assessment, and that the result would approximate a linear dose-response curve down to zero exposure (see Lynch *et al.* 2017a for further discussion of the effect of high-dose data on the dose-response relationship).

The agency rejects the use of MOA analysis to develop the dose-response relationship because the agency believes it can develop this adequately by simply using the epidemiological data in a more sophisticated manner than in 2010. However, multiple commenters indicated that this was inconsistent with the NRC recommendations, and it would likely lead again to an overestimated linear dose-response relationship.

The problem formulation statement needs to straightforwardly describe the threshold MOAs developed in the literature and the conforming epidemiologic data, rather than ignore them. EPA needs to acknowledge that "the presence of a threshold relationship between iAS exposure and cancer in human studies is supported by the animal and *in vitro* MoA data showing carcinogenic effects of iAs at tissue concentrations corresponding to those expected from about 100 ug/L iAs in drinking water." Lynch *et al.* 2017a. Contrast this with the paucity of evidence supporting a genotoxic MOA, which is the only known MOA that would be consistent with a linear no-threshold approach. The Arsenic Science Task Force comments flatly state that "all the possible modes of action lead to the same conclusion that the dose-response has a threshold." Also, EPA 's own pesticide office had affirmed a threshold MOA for dimethylarsinic acid (DMA5), an organic arsenical compound, with little controversy several years ago. The National Center for Environmental Assessment office (NCEA) may be out of step with the other EPA offices.

EPA declined to produce an evidence synthesis of bladder, lung and skin cancer because "the strength of evidence for these health outcomes was considered *robust." Protocol at 13.* However, it is quite clear that the agency would benefit from such a synthesis focusing on the low-dose region for these health endpoints. The protocol evidences no serious familiarity with the literature cited by the commenters, and instead relies on the secondary

literature: all government studies. ATSDR 2016, NTP 2016, IARC 2012, WHO 2011a,b: ASTDR 2007; IARC 2004b. *Id.* In short, EPA needs to develop a systematic review protocol that reviews the literature comprehensively, and not simply rely upon the government sponsored analyses. The protocol omits mention of the substantial literature that address low doses and relies on analyses that were dominated by high dose data – exactly what the NRC advised EPA not to do.

This raises the question of how adequate the systematic literature review was, and whether it needs to be refined further. A discussion of one of the most important papers, "Dose-response for assessing the cancer risk of inorganic arsenic in drinking water: the scientific basis for the use of a threshold approach", sponsored by the Texas Commission on Environmental Quality, is missing (although noted in the bibliography). Tsuji *et al.* 2019. The Department of Defense comments note that "the absent documents appear to be those that support an analysis of the data that is inconsistent with EPA's previous conclusions," although I'm sure that neither DOD or any other commenter had the time with a 30 day comment period to investigate this thoroughly.

EPA further reports that "a MOA analysis to address potential differences in response across human populations was not considered essential." While it may not be "essential", EPA fails to explain why it would disregard a MOA analysis. *Protocol Section 2.3.2*

Dr. Tsuji illustrates why EPA's current plan to ignore the MOA in dose-response modeling is problematic. "It is important to recognize that a time-averaged dose that includes a short period of high-dose exposure is not toxicologically equivalent to a more constant average dose. Mechanistically, high past exposures in excess of effect levels (e.g., 100 to 150 µg/L in drinking water or 0.1 µM at the cellular level; Tsuji *et al.* 2019) may have resulted in adverse outcome pathways leading to later increased risk of disease. This example further illustrates the importance of incorporating mode of action information in interpreting epidemiological studies." Tsuji Comments at 3. EPA is bound to overestimate the dose-response relationship it considers data on both sides of a threshold but fails to address this discontinuity.

In sum, EPA needs to perform a synthesis of the evidence regarding *low dose* cancer and noncancer effects and to take into account the existence of a possible threshold in developing the dose-response curves for inorganic arsenic. The NRC needs to provide clear and firm instructions to EPA to avoid the need for yet another revision in this decades long saga.

On a related note, EPA should initiate plans to implement steps 2 and 3 of the IRIS process, and not simply skip from step 1 formulation to step 4 assessment (the current plan dated April 2019), given the major public concerns. EPA would benefit significantly from advice regarding evidence synthesis at low dose and a comprehensive discussion of the critical issues which occur at steps 2 and 3. We continue to recommend use of the highly transparent and robust 2013 IRIS steps, which clearly would improve this

controversial assessment. This recommendation is submitted for consideration by EPA, although the NRC committee may be interested in commenting on this option.

We encourage the NRC committee members to consider carefully the public comments submitted to the NRC and the EPA docket. The agency needs to comprehensively address all available data, perform a synthesis of the low dose and mode-of-action literature, and take care not to extrapolate from high dose data. This is critical to a robust review of these issues. For your convenience, I have selected some key comments from two commenters below for your use.

Comments from the US Department of Defense:

1. While EPA may choose which data and analyses it wishes to adopt, published analyses that present alternative conclusions should also be presented in the evaluation to be clear and transparent. Listed below are some of these concepts that are not presented in this draft that are discussed in one of the journal articles (Lynch *et al.* 2017) cited in this Problem Formulation. "The sensitivity analyses we conducted suggested that populations with relatively high iAs exposures appeared to drive the pooled cancer risk estimates" "The most robust iAs datasets come from populations with very high exposures (predominantly in South Asia and South America) .... Differences in factors that affect the true iAs dose among populations, including cooking methods and dietary patterns, water intake, nutritional deficiencies, and metabolic factors, all complicate the application of many key studies when determining the most appropriate exposure metric for use in risk assessment (e.g., urinary iAs levels, average water iAs concentration, various cumulative measures) and extrapolating risk estimates from one population to another (NRC, 2013; Chu and Crawford-Brown, 2006). Ultimately, these issues affect the ability to draw conclusions regarding potential cancer risks from iAs exposure in American populations." Additionally, "The presence of a threshold relationship between iAs exposure and cancer in human studies is supported by the animal and in vitro MoA data showing carcinogenic effects of iAs at tissue concentrations corresponding to those expected from about 100 µg/L iAs in drinking water. Under this interpretation, all exposures to iAs concentrations below this level are without any increased cancer risk."

2. The text [at 2.3.2] states: "a MOA analysis to address potential differences in response across human populations was not considered essential." This statement is in conflict with the NRC analysis that states, "On the basis of the extensive epidemiologic data, the committee expects that the results of animal and in vitro mechanistic studies will facilitate the understanding of the biologic plausibility or mechanisms of arsenic causation of effects observed in epidemiologic studies and interpretation of low-dose effects ..." MOA analyses could provide essential information as to the differences in response in the human

populations that would elucidate the underlying dose-response function in humans and how confounding factors such as co-exposures, diet, etc., affected the response.

3. The first paragraph [text at 2.3.2] omits the major function of a mode-of-action (MOA) analysis under EPA's 2005 cancer guidelines which is to determine whether there is a threshold for carcinogenesis below which exposures are not expected to cause cancer. The first mention of MOA in the guidelines is on page 1-9 where the discussion is solely about extrapolation to lower levels of exposure, and no reference is made to whether the data are from animals or humans. The third sentence in section "1.3.2. Mode of Action" discusses use of MOA analyses "in animals or humans". As the existence of a threshold for inorganic arsenic has been a major topic of discussion for over a decade, the omission of this significant purpose for a MOA analysis is a major omission.

4. "Concern over not using MOA analyses in dose-response analysis is offset by ..." This sentence assumes the procedures listed are more accurate than information from MOA. They are complementary and should be used together. If the results are consistent, then confidence is increased. Moreover, this statement is inconsistent with NRC (2013) that states: "Mode-of-action analyses should be used to inform dose-"response modeling with respect to the shape of the curve, particularly in the low dose region ..." Note particularly that NRC mentions the shape, not extrapolation. EPA's extensive listing of why the MOA analysis that was conducted should nevertheless be ignored lacks clarity and transparency and suggests that inclusion might weaken, or possibly contradict, the conclusions in this document. Since a major consideration in EPA's 2005 cancer guidelines is the use of MOA analyses, EPA should not only present its analysis in and appendix, but also demonstrate in the main text how its results/conclusions would differ if MOA were used. Only after a full, clear, and transparent presentation of both options should EPA opine on its selection based either solely on science or on a combination of science and science policy. By rejecting MOA before presenting the potential effects, EPA does not allow an independent reviewer to draw conclusions as to the validity or effect of these decisions without substantial additional scientific analyses -- which many reviewers do not have the resources to perform.

5. The text of this section, specifically that the expected results for carcinogenicity will be either an OSF or IUR, assumes that MOA for carcinogenicity will not have a threshold. Since these statements are made prior to the evaluation of the data, they could be considered biased. Since this section states that the dose-response functions may be non-linear and since previous statements in the document indicate that the data will be in the range of human exposure (not extrapolated), we note that EPA's 2005 cancer guidelines require the use of RfD/C for all nonlinear dose-response functions even when no threshold has been established. The footnote on page 1-11 of the cancer guidelines states: "The term "nonlinear" is used here in a narrower sense than its usual meaning in the field of mathematical

modeling. In these cancer guidelines, the term "nonlinear" refers to threshold models (which show no response over a range of low doses that include zero) and some nonthreshold models (e.g., a quadratic model, which shows some response at all doses above zero)."

6. Missing from this section [Appendix A], as well as the main text, are [the NRC] comments and recommendations about the utility of MOA for both analysis and transparency. A few quotes are: "Mode-of-action analysis should be applied to organize and synthesize data and to harmonize cancer and noncancer end points, especially in the case of arsenic, on which there are large data gaps in regions of the dose-response relationship in key areas and low-dose exposures of regulatory concern. ... An emphasis on hazard characterization is warranted and can be achieved by using a mode-of-action approach in which the necessary key events for the pathogenesis of each health outcome are examined in a dose-dependent and time-dependent manner." "Such a mode-of-action assessment can be particularly helpful in the analysis of potential confounding effects, of the role of simultaneous exposure to other agents or actions, and of individual risks and population susceptibilities." "Arsenic's action is complex, and many mechanisms of action and several possible modes of action have been assessed in the context of exposure of humans to high doses through drinking water. It is generally accepted that arsenic is not directly mutagenic but rather acts via an indirect mechanism that involves secondary mediators (such as oxidant damage, modified proteins, and immune suppression)." "The key aspect of mode-of-action analysis is that it provides an evidence-based assessment, integration, and synthesis of all the available data on a chemical, its adverse health effects, and its biology."

Comments from Gradient:

1. Failing to deal adequately with such low-exposure applications is the reason that EPA's past attempts to finalize an iAs assessment have faltered and have failed to win the confidence of reviewers, including the review by a special National Research Council (NRC) committee. If this next revision of the EPA assessment is to succeed, it needs to explicitly, forthrightly, and credibly address the basis for asserting any conclusions about the potential for low exposures to iAs to cause health impacts, rather than simply relying on "upper bound" projections from effects at much higher exposures.

2. Analysis of those epidemiology studies, however, shows that they provide essentially no support for the existence of risks at low iAs exposure levels, much less the ability to quantify such risk potential. There are enough studies with enough low-exposure dose points to show that, as one goes upward in exposure from low doses, there are no apparent effects and no real evidence of upward trends in cancer risks until exposures get higher than those resulting from water concentrations of over 100 µg/L. In general, human studies that have focused on the lower-level exposures that prevail in most parts of the world have shown little evidence of cancer risks. It is also worth noting that low-dose exposures estimated from iAs levels in drinking water do not account for

other sources of iAs (*e.g.*, from the diet) and, therefore, may be underestimating total iAs exposure.

3. In particular, a paper of ours cited by the Problem Formulation (Lynch *et al.*, 2017) showed that inferences of risks at lower iAs doses depends on the effect of high doses "pulling up" the whole dose-response curve, and examination of low doses in epidemiology studies of bladder cancer risk do not provide indications, much less evidence, of the existence of low-dose risk elevation. A number of other recent published analyses of epidemiological data for iAs and cancer have reached similar conclusions.

4. We see it as a mistake to assert that a mode-of-action argument needs to be definitive and exclusionary of any alternative approach before it can be presented as an informative analysis. As we have stated, the epidemiology does not directly demonstrate the existence of low-dose cancer risks for iAs, and indeed, it seems to show a lack of such effects, tempered by consideration of statistical power. Elevating an upper-bound projection of epidemiology from high doses over analyses of investigated and demonstrable biological effects at the relevant low-dose range as provided in mode-of-action studies would result in an assessment that fails to address the key questions that will arise as it is applied in most regulatory settings. We fear it would only result in a call for yet another round of revisions of the assessment. In short, all available bases for inferences about low-dose risk possibilities need to be considered, and a lack of definitive proof should not be used as an excuse to invoke an unsupported linear projection from high doses.

References:

Lynch HN, Zu K, Kennedy EM, Lam T, Liu X, Pizzurro DM, Loftus CT, Rhomberg LR. 2017a. Quantitative assessment of lung and bladder cancer risk and oral exposure to inorganic arsenic: Meta- regression analyses of epidemiological data. Environment International, 106: 178–206.

Tsuji, JS, ET Chang, PR Gentry, HJ Clewell, P Boffetta and SM Cohen. 2019. Dose-response for assessing the cancer risk of inorganic arsenic in drinking water: the scientific basis for use of a threshold approach, Critical Reviews in Toxicology, DOI: 10.1080/10408444.2019.1573804